Less than 1% of CD19+ and CD11b+ donor splenocytes originated from OP9-DL1 T-cell precursors. In our preliminary experiments we did so far not observe any signs of graft-versus-host disease (GVHD) in recipients of OP9-DL1 T-cell precursors. The proliferative capacity of splenic T cells as determined by third-party MLR was intact compared to controls. We conclude that the co-culture of HSC with OP9-DL1 cells and growth factors results in a 850- to 5000-fold expansion of > 95% pure T-cell precursors, which can home to the thymus after infusion into allo HSCT recipients. These precursors undergo normal T-cell development, reconstitute the periphery, proliferate to third party antigens, do not cause GVHD, and improve donor T-cell chimerism. Therefore, adoptive transfer of OP9-DL1 derived T-cell precursors could significantly enhance posttransplant T-cell reconstitution without GVHD.

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PHASE I STUDY OF A NEUTRALIZING MONOCLONAL ANTI-CTLA4 ANTIBODY (MDX-010) IN PATIENTS WITH RELAPSE OF MALIGNANCY AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Relapse of malignancy remains a major cause of treatment failure after allogeneic hematopoietic stem cell transplantation (allo-HCT). Tumors may utilize a variety of mechanisms to evade the adoptive immunotherapy provided by allo-HCT. These may include lack of costimulation and direct or indirect inhibition of T-cell activation. CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) is a homologue of CD28 that functions as a negative regulator of T-cell activation. Blockade of CTLA-4 using neutralizing antibodies has demonstrated potent anticancer effects in animal models of antitumor immunity. Tumor regression as well as autoimmune phenomena have been seen in phase I/II clinical trials of CTLA-4 blockade in advanced solid tumors. Although CTLA-4 blockade may augment graft-versus-malignancy after allo-HCT, GVHD and other immune complications may also be increased. We have conducted a phase I dose-escalation trial of a neutralizing human monoclonal anti-CTLA-4 antibody (MDX-010) in patients with relapse of malignancy after allo-HCT. Eligibility criteria included allo-HCT ≥ 90 days previously, > 50% donor T-cell chimerism, no prior grade 3/4 GVHD, and no prophylaxis/therapy for GVHD for ≥ 6 weeks. Eligible patients received a single dose of MDX-010 over 90 minutes. Patients were allowed DLI at a dose of 5×10^6 CD3 cells/kg 8 weeks after MDX-010 if no GVHD occurred and progression of malignancy (PD) was present. Six patients (3 males and 3 females; median age 44 years; 2 cases of CML, 1 case of AML, 1 case of myeloma, 1 case of renal carcinoma, 1 case of breast cancer) have been treated (4 at a dose level of 0.1 mg/kg, 3 at a dose level of 0.33 mg/kg). MDX-010 was well tolerated in this setting; no infusional toxicity was seen. No patient has developed clinically significant exacerbation of GVHD or new-onset GVHD after infusion. One patient (dose, 0.1 mg/kg) developed a grade 3 polyarthropathy with rheumatoid nodules 14 weeks after MDX-010 and 6 weeks post-DLI, which resolved with corticosteroid therapy. No other autoimmune complications were seen. MTD has not been reached. Two patients have demonstrated possible anticancer responses (ie, partial remission of AML refractory to prior therapies, molecular remission of CML maintained off imatinib). With a median follow-up of 164 days, 1 patient has died (PD), 5 patients are alive, and 1 patient is in CR. Pharmacokinetic and correlative science data will be presented. This study shows safety with possible antitumor effects at the dose levels tested.

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A PILOT STUDY EVALUATING THE SAFETY AND EFFICACY OF AMD3100 FOR THE MOBILIZATION AND TRANSPLANTATION OF HLA-MATCHED SIBLING DONOR HEMATOPOIETIC STEM CELLS IN PATIENTS WITH ADVANCED HEMATOLOGICAL MALIGNANCIES

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Cytokine-mobilized peripheral blood (MPB) has become the preferred allograft source for patients with advanced hematological malignancies. Procurement of MPB currently requires from 5 to 6 days of granulocyte colony-stimulating factor (G-CSF) administration and is associated with donor morbidity and high cost. Recent studies suggest G-CSF induces mobilization by indirectly targeting the interaction between the chemokine stromal derived factor 1 (SDF-1) and its receptor CXCR-4. Here we report preliminary results using a direct antagonist of the SDF-1/CXCR-4 interaction, AMD3100, as a single agent to procure MPB from allogeneic donors in only 1 or 2 days. Four HLA-identical siblings, all males ranging from 40 to 58 years old, received 1 or 2 doses of AMD3100 at 240 μg/kg, followed 4 hours later by leukapheresis (LP). After collection and a 1-week washout period, the same donors were remobilized using G-CSF at 10 μg/kg/day, followed by LP commencing on day 5. The target CD34+ cell dose following each agent was > 2.0×10^6/kg recipient weight. The results of the mobilizations and allograft composition are presented in the table. After AMD3100, all donors tolerated treatment well, and none experienced greater than grade 1 toxicity. All donors experienced grade 2 bone pain during G-CSF mobilization. The AMD3100-mobilized cells from 2 donors (donors 1 and 4) were transplanted into a 51-year-old woman with AML and into a 48-year-old woman with NHL, respectively, after conditioning with cyclophosphamide (120 mg/kg) and total body irradiation (single 550-cGy dose). Both recipients engrafted neutrophils > 500/μl promptly on days +10 and +11 and platelets > 20,000/μl on days +14 and +20. Both patients are currently being followed as outpatients and are without GVHD. The patient with AML has full donor chimerism and normal trilineage hematopoiesis over 4 months following transplant and is in complete remission. The allografts collected from 2 donors were not given due to progressive disease in the intended recipients. Grafts mobilized after AMD3100 differ from G-CSF-mobilized allografts in the content of CD34+ and immune effector cells but appear to reconstitute hematopoiesis similarly. These preliminary data suggest that a chemokine antagonist can safely and rapidly induce the mobilization of a functionally competent hematopoietic allograft. Accrual is ongoing, and additional donor/recipient pairs will be presented.

Results of Mobilization						
Agent	AMD3100	AMD3100	AMD3100	AMD3100	AMD3100	G-CSF
Donor #	1	2	3	4	Combined Median Values	4 Combined Median Values
Days of drug administration	2	1	2	2	2	5
# LP Procedures	2	1	2	2	2	1
Peak fold ↑ CD34	7	6	7	5	6.5	22
CD34 dose ($\times 10^6$/kg)	2.6	2.1	1.2	2.5	2.3	2.9
CD3 dose ($\times 10^8$/kg)	4.9	1.5	2.7	3.2	3.8	1.3
CD4 dose ($\times 10^8$/kg)	3.1	1.0	2.0	3.2	2.5	0.8
CD8 dose ($\times 10^8$/kg)	1.7	0.4	0.6	3.4	1.2	0.5
CD56 dose ($\times 10^7$/kg)	3.4	2.1	2.7	3.7	3.1	1.9